

## Value of Radionuclide Rest and Exercise Left Ventricular Ejection Fraction in Assessing Survival of Patients After Thrombolytic Therapy for Acute Myocardial Infarction: Results of Thrombolysis in Myocardial Infarction (TIMI) Phase II Study

BARRY L. ZARET, MD, FACC, FRANS J. TH. WACKERS, MD, FACC,

MICHAEL L. TERRIN, MD, MPH,\* SANDRA A. FORMAN, MA,\* DAVID O. WILLIAMS, MD, FACC,†

GENELL L. KNATTERUD, PhD,\* EUGENE BRAUNWALD, MD, FACC,‡ FOR THE TIMI STUDY GROUP

New Haven, Connecticut; Baltimore, Maryland; Providence, Rhode Island; and Boston, Massachusetts

**Objectives.** This study sought to determine the prognostic value of rest and exercise left ventricular ejection fraction in patients receiving thrombolytic therapy as part of the Thrombolysis in Myocardial Infarction (TIMI) trial.

**Background.** In the prethrombolytic era, ejection fraction at rest as well as during exercise was an important prognostic index in patients recovering from acute myocardial infarction. The prognostic value of these measurements in the thrombolytic era is not clear.

**Methods.** As part of the TIMI II protocol, we obtained radionuclide left ventricular ejection fraction at rest and during symptom-limited submaximal supine exercise. Measurements were related to 1-year all-cause as well as cardiac mortality. In addition, the relation between ejection fraction obtained at rest and 1-year cardiac mortality in this study was compared with the relation established previously in the prethrombolytic era by the Multicenter Postinfarction Research Group.

**Results.** A distinct relation was noted between left ventricular

ejection fraction at rest and all-cause mortality. The highest mortality rate (9.9%) was noted in patients with an ejection fraction <30%. Those not undergoing a study had a 1-year mortality rate of 6.2%. Peak exercise ejection fraction provided prognostic information similar to that of rest ejection fraction. Likewise, change in ejection fraction from rest to exercise did not appreciably improve prognostic impact.

**Conclusions.** Rest left ventricular ejection fraction is an important prognostic index in patients receiving thrombolytic therapy. Peak exercise ejection fraction and the change in ejection fraction from rest to exercise do not provide appreciable prognostic data beyond those obtained at rest. Patients unable to exercise or those not having a rest study have a poor prognosis. When compared with the Multicenter Postinfarction Research Group data, there was strong evidence of a difference in survival in the two studies. At any level of ejection fraction, mortality was lower in TIMI II patients than in patients in the prethrombolytic era.

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In the prethrombolytic era, left ventricular ejection fraction at rest and during peak exercise and the difference between peak exercise and rest ejection fraction were important prognostic indexes in both postinfarction patients and patients with stable coronary disease (1-12). It has been suggested (13) that the effect of coronary reperfusion on survival and left ventricular function may not be related. That is, enhanced survival after thrombolytic therapy may not be associated with concomitant

improvement in ventricular performance. It has also been suggested (14) that left ventricular ejection fraction should not be considered a surrogate end point of trials of thrombolytic or adjunctive therapies, or both, for establishing myocardial reperfusion. Some questions about the utility of ejection fraction measurements concern the relation of global to regional function as well as the temporal sequence of improvement in function after reperfusion (14).

In the Thrombolysis in Myocardial Infarction Phase II (TIMI II) clinical trial, patients presenting with ST segment elevation who were recruited within 4 h of the onset of chest pain were treated with intravenous recombinant tissue-type plasminogen activator (rt-PA) and were randomly assigned to either an invasive or conservative treatment strategy and treated with intravenous heparin and aspirin. At the time of hospital discharge, radionuclide ventriculography was performed at rest and during exercise. The purpose of the present report is to evaluate 1-year survival on the basis of rest and exercise radionuclide left ventricular function assessed in this

From the Departments of Cardiovascular Medicine, Yale University School of Medicine, New Haven, Connecticut; \*Mayland Medical Research Institute, Baltimore, Maryland; †Brown University School of Medicine, Providence, Rhode Island; ‡Harvard University School of Medicine, Boston, Massachusetts. A complete list of TIMI co-investigators and participating institutions appears in reference 15. This study was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

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**Address for correspondence:** Dr. Barry L. Zaret, Chief, Cardiovascular Medicine, Department of Internal Medicine, Yale University, 333 Cedar Street, New Haven, Connecticut 06520-8017.

large group of patients with acute myocardial infarction undergoing thrombolytic therapy. These prognostic data are compared with those obtained in the prethrombolytic era.

## Methods

**Study protocol.** The details of the TIMI II protocol have been described elsewhere (15). Briefly, eligibility criteria were age <76 years, chest discomfort characteristic of myocardial ischemia lasting  $\geq 30$  min, ST segment elevation  $>0.1$  mV in two contiguous electrocardiographic (ECG) leads, no contraindication to thrombolytic therapy, feasibility of instituting such therapy within 4 h of onset of chest pain and patient consent. Patients received a 6-h infusion of rt-PA (alteplase [Activase] supplied by Genentech, Inc.) and were randomly assigned to either invasive or conservative strategies.

Patients assigned to the invasive strategy were scheduled for coronary angiography and angioplasty, if feasible, 18 to 48 h after study entry. Coronary artery bypass surgery was recommended for invasive strategy in patients with coronary anatomy that was too complex or hazardous for angioplasty. Patients assigned to the conservative strategy underwent these procedures for spontaneous or provoked myocardial ischemia. Concomitant therapy included intravenous infusion of heparin and daily administration of aspirin tablets. Patients eligible for enrollment in a beta-adrenergic blocking agent therapy study (TIMI IIB) were also randomly assigned to receive either immediate intravenous or delayed oral administration of metoprolol (16).

Research nurse-coordinators from each participating clinical center were trained and certified in data collection, recording and data transfer to the coordinating center. For each patient, outcome was determined at the time of hospital discharge and 6 weeks, 6 months and 1 year after enrollment through clinic visits or telephone interview, or both.

**Rest-exercise equilibrium radionuclide ventriculography.** Radionuclide-derived left ventricular ejection fraction was measured according to protocol in all patients. The protocol hospital discharge study was obtained an average of 9.3 days after study entry (range 2 to 38). Equilibrium radionuclide ventriculography was performed after modified in vivo red blood cell labeling according to standardized techniques (17,18). To ensure quality of data, before clinical participation in TIMI II began, each site was certified on the basis of provision of radionuclide studies of acceptable quality.

Radionuclide ventriculography studies were initially obtained at rest, with the patient in the recumbent position. Thereafter, the patient was prepared for supine bicycle exercise. Repeat 2-min baseline measurements at rest were acquired with the patient's feet placed on the pedals of the bicycle ergometer. Radiolucent chest lead electrodes were used for ECG gating and monitoring during exercise. Exercise was begun at a work load of 200 kilopond-meters (kpm) and increased by 200 kpm after each 3-min stage. The exercise test at hospital discharge was limited to a maximal rate of 120

beats/min, a maximal work load of 400 kpm or by development of angina or  $>2$  mm ST segment depression, whichever came first. Ventricular function measurements were obtained during the last 2 min of each 3-min stage of exercise.

All data were acquired in ECG synchronized frame mode at 16 frames/RR interval in a  $64 \times 64$  matrix. The unsmoothed studies were stored on magnetic tape or floppy disks and were submitted to the radionuclide core laboratory for further analysis. In the core laboratory at Yale University, studies were transcribed to a central computer facility for temporal and spatial filtering and processing. Global left ventricular ejection fraction was determined from the image recorded in left anterior oblique view using previously standardized and validated computer programs (17,18). The left ventricular volume curve corrected for background was filtered using four Fourier harmonics. Left ventricular ejection fraction was determined from the generated volume curve in the usual manner. In addition, regional function was assessed by measurement of regional ejection fraction from the same study.

**Statistical methods.** Because survival through 1 year was comparable and global ejection fraction was similar for the two treatment strategies (invasive and conservative), data from both patient groups were combined in analyzing prognosis on the basis of radionuclide ventriculographic measures of left ventricular function. Survival was estimated using the product limit method (19), with p values taken from log-rank tests (20). For comparison with the published data of the Multicenter Postinfarction Research Group, TIMI II ejection fraction data were reclassified into four categories ( $>60\%$ ,  $40\%$  to  $59\%$ ,  $20\%$  to  $39\%$  and  $<20\%$ ) (1). For both studies, 99% confidence intervals for the proportion of patients who died in each category were calculated using standard methods (21). A logistic regression model, including ejection fraction category, research project (Multicenter Postinfarction Research Group [MPRG] or TIMI II) and an interaction term (ejection fraction by research project), was used to compare the mortality between the studies, taking into account differences in ejection fraction (22).

To adjust for multiple comparisons, p values between 0.01 and 0.001 for two-sided tests were specified as providing some evidence of differences, and  $p < 0.001$  as providing strong evidence of differences. These analyses were performed using Statistical Analysis System (SAS) programs (23). The prognostic value of radionuclide ventriculographic variables and baseline characteristics were evaluated using Cox proportional hazards regression models (24) and Biomedical Data Package (BMDP) programs (25). Patient characteristics included in these models were gender, race, previous infarction, infarct location (anterior or nonanterior), history of angina, history of congestive heart failure, history of hypertension, history of diabetes, presence of painful ischemia (chest pain reported to the clinical center staff by the patient) at the time of initiation of thrombolytic therapy, age and time from onset of symptoms to treatment. Analyses were based on the final TIMI II data file.

**Table 1.** One-Year All-Cause Mortality Versus Rest Ejection Fraction at Hospital Discharge

Rest EF at Hospital Discharge (%)	No. of Pts	No. (%) of Deaths	99% CI
No study	630	39 (6.2)	4.2-9.2
<30	162	16 (9.9)	5.3-18.0
30-39	355	11 (3.1)	1.4-6.6
40-49	604	13 (2.2)	1.1-4.4
50-59	835	10 (1.2)	0.5-2.7
≥60	611	8 (1.3)	0.5-3.2
Total	3,197	97 (3.0)	2.4-3.9

CI = confidence interval; EF = ejection fraction; Pts = patients.

## Results

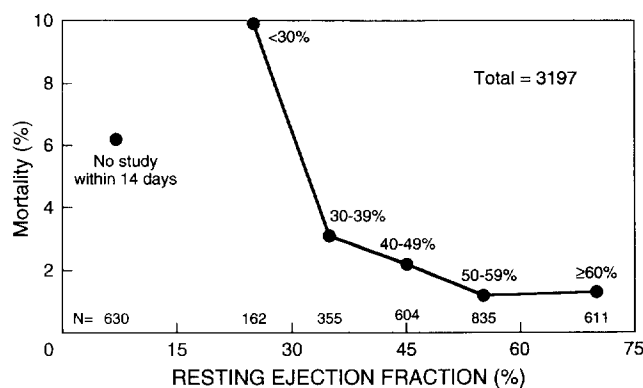
**Patient population.** Of the total of 3,339 patients enrolled in TIMI II, 1,681 were randomly assigned to the invasive strategy, and 1,658 to the conservative strategy. The baseline clinical characteristics of patients in each strategy were comparable (15). A total of 142 patients died before 14 days and did not have a radionuclide ventriculographic study. The remaining 3,197 patients form the prognostic study cohort.

The vital status of all patients was known at 6 weeks from study entry. Follow-up at 1 year for mortality was complete for 99.3% of patients. There were 97 deaths in the patient cohort; 75 were attributed to cardiovascular causes. There were eight noncardiac deaths; of these six were related to malignancies. Thirteen deaths occurred from complications of therapy, including hemorrhagic stroke. Precise circumstances of one patient's death are not available to us.

**Availability of radionuclide ventriculographic data.** In 772 patients no or incomplete radionuclide ventriculographic data were available 14 days after study entry. In 187 of these patients the radionuclide ventriculogram was obtained after 14 days. In 212 patients a radionuclide ventriculogram was obtained within 14 days, but ejection fraction could not be measured for technical reasons. In 74 patients, radionuclide ventriculography was not performed because of recent coronary bypass surgery. In 157 patients no radionuclide ventriculography was performed because of unstable cardiac status in 51 or logistic considerations in 106, or both. The proportion of patients who did not survive 1 year in these groups ranged from 2.7% to 12.1%. The radionuclide ventriculographic data were available for a total of 2,567 patients.

**Relation of mortality to rest left ventricular ejection fraction.** The relation between all-cause mortality and rest hospital discharge left ventricular ejection fraction is illustrated in Table 1 and Figure 1. The highest mortality rate (9.9%) was noted in patients with ejection fraction <30%. Ejection fraction >30% was associated with a relatively low 1-year mortality rate (range 1.2% to 3.1%). Of note, the 1-year mortality rate was 6.2% in those patients not undergoing study for any reason.

Mortality varied, however, according to the reasons for missing radionuclide ventriculographic data. Those patients



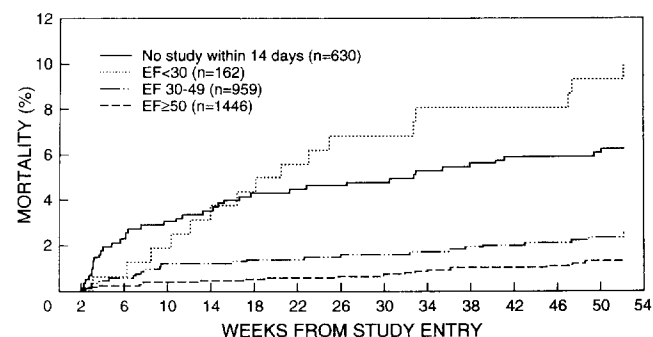
**Figure 1.** Relation of rest ejection fraction to all-cause mortality in the TIMI II study. Note the hyperbolic shape of the curve and the mortality rate for patients who did not undergo radionuclide ventriculography within 14 days.

having a study >14 days after study entry had a 2.7% mortality rate through 1 year from study entry. Those not undergoing radionuclide ventriculography because of a recent operation had an 8.1% mortality rate, and those not having a study for various cardiac and logistic reasons had a 12.1% mortality rate. Those with technically poor studies had a 4.2% mortality rate. Similar findings were noted for cardiovascular mortality and all-cause mortality.

Kaplan-Meier analyses indicated a high early mortality in those patients who did not undergo radionuclide ventriculographic study as well as in those with an ejection fraction <30% (Fig. 2). There was a relatively low mortality rate in patients with an ejection fraction >30%. There was little difference between those with an ejection fraction of 30% to 49% and those with an ejection fraction ≥50%. Most deaths occurred within the first 6 weeks of study entry.

**Relation of mortality to exercise ejection fraction.** Peak exercise ejection fraction was also evaluated as a prognostic index (Table 2). A total of 1,045 patients had no exercise study within 14 days. The mortality rate was high in this group (5.8%). For patients who did exercise, the peak exercise radionuclide ventriculogram provided prognostic information

**Figure 2.** Kaplan-Meier analysis of mortality rate related to time from study entry, with patients categorized according to ejection fraction (EF). Mortality rate is highest in patients with ejection fraction <30%.



**Table 2.** One-Year All-Cause Mortality Versus Exercise Ejection Fraction at Hospital Discharge

Exercise EF at Discharge (%)	No. of Pts	No. (%) of Deaths	99% CI
No study	1,045	61 (5.8)	4.2-8.0
<30	116	6 (5.2)	1.8-14.1
30-39	226	10 (4.4)	2.0-4.7
40-49	418	8 (1.9)	0.8-4.7
50-59	573	4 (0.7)	0.2-2.5
≥60	819	8 (1.0)	0.4-2.4
Total	3,197	97 (3.0)	2.4-3.9

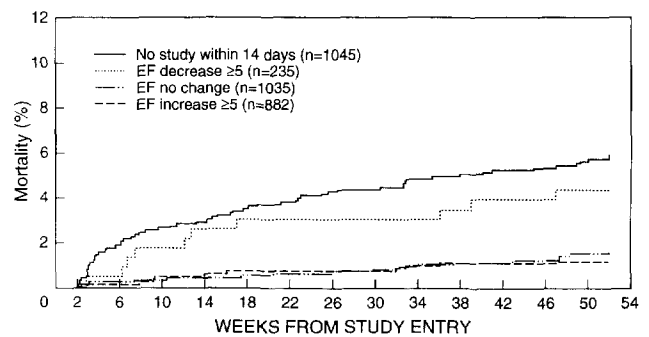
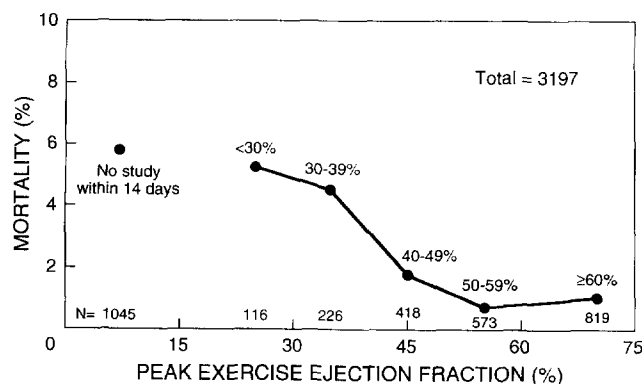
Abbreviations as in Table 1.

similar to that provided by the rest ejection fraction (Fig. 3). Decrease in ejection fraction with exercise was associated with increased mortality (Fig. 4).

**Multivariate analysis.** In the 2,567 patients with radionuclide ventriculographic data at rest, ejection fraction was inversely associated with 1-year mortality: Lower ejection fraction was associated with increased mortality (Cox model coefficient  $-0.048$  per unit of ejection fraction,  $p < 0.0001$ ). Inability to exercise was also associated with mortality (Cox model coefficient  $-1.045$ ,  $p < 0.001$ ). Peak exercise ejection fraction and change in ejection fraction from rest to exercise did not appreciably improve the predictive accuracy. In those patients with both rest and exercise data ( $n = 2,143$ , 1-year mortality rate 1.7%), rest ejection fraction remained the important predictor of mortality (Table 3). Of clinical variables, diabetes mellitus had the most important association with mortality.

## Discussion

**Prognostic value of ejection fraction.** The overall 1-year mortality in TIMI II is low. As reported previously, except for those patients with a previous myocardial infarction, no differences in mortality exist between invasive and conservative strategy groups, either at hospital discharge or at 1 year follow-up (15,26). Our data demonstrate several relevant

**Figure 3.** Relation of all-cause mortality to peak exercise ejection fraction. Note again the hyperbolic shape of the survival curve and the impact of nonperformance of radionuclide ventriculography on subsequent mortality.**Figure 4.** Kaplan-Meier analysis of the relation between mortality rate and time from study entry on the basis of ejection fraction (EF) response to exercise. Note that the highest mortality occurs in those patients who did not undergo radionuclide ventriculography or who demonstrated a significant decrease in ejection fraction.

findings. 1) Rest left ventricular ejection fraction, first identified as an important prognostic index before the advent of thrombolytic therapy, also retains its importance in patients who have received this treatment. 2) Peak exercise ejection fraction and the change in ejection fraction from rest to exercise do not provide appreciable prognostic data beyond that obtained from the rest ejection fraction alone. 3) Although heterogeneous as a group, patients unable to exercise or who did not have a rest radionuclide ventriculographic study have a poor prognosis. 4) At any level of ejection fraction, mortality was lower in the TIMI II cohort than that observed in patients in the prethrombolytic era (MPRG). Thus, ejection fraction in patients receiving thrombolytic therapy still appears to provide relevant prognostic information. However, a normal or modestly impaired ejection fraction is associated with an exceedingly low mortality rate in this patient population.

Ejection fraction is easily measured noninvasively by routine radionuclide techniques, and high quality reproducible data can be obtained routinely without the technical difficulties and invasive nature of contrast angiography, including complicating ventricular ectopic beats. Furthermore, the geometry independence of count-based measurements adds to the reliability and reproducibility of radionuclide ventriculographic assessments, particularly in patients with myocardial infarction and distorted ventricular geometry.

### Relation of preserved ventricular function and survival.

Although there is a demonstrable relation between the overall level of global left ventricular function as measured by ejection fraction and mortality, there nevertheless exists discordance between preservation of ventricular function and survival in patients treated with thrombolytic therapy. That is, enhanced survival may occur despite impaired systolic function. A number of explanations have been offered for this disparity, including the so-called time-to-treatment paradox (13,15). It can be argued that early administration of thrombolytic therapy may salvage patients with very poor ventricular function who would otherwise have died if they had not received thrombolysis or if they had been treated later in the course of their infarction. In analyses limited to surviving patients, the

**Table 3.** Relation of Mortality to Baseline Variables and Rest Ejection Fraction at Hospital Discharge and Change in Ejection Fraction (exercise minus baseline) for 2,143 Patients

Variable	Coefficient*	p Value
Rest EF at hospital discharge	-0.036	0.01
Change in EF (exercise - baseline)	-0.040	0.11
Male (vs. female)	-0.433	0.23
White (vs. nonwhite)	-0.567	0.19
Prior MI (vs. no prior MI)	0.721	0.06
Anterior MI (vs. nonanterior MI)	-0.328	0.37
History of angina (vs. no history of angina)	0.706	0.10
History of CHF (vs. no history of CHF)	-0.458	0.66
History of hypertension (vs. no history of hypertension)	0.400	0.25
History of diabetes (vs. no history of diabetes)	0.930	0.01
Pain at time of treatment initiation (vs. no pain at time of treatment initiation)	0.148	0.78
Age (10-yr increments)	0.493	0.02
Time from onset of symptoms to treatment $\leq 2$ h (vs. $> 2$ h)	0.079	0.84

\*Positive coefficients are associated with increased mortality for the first named of dichotomous variables, negative coefficients with increased mortality for the alternate (in parentheses). The positive coefficient for age indicates increasing mortality with increasing 10-year age intervals. The negative coefficient for rest ejection fraction (EF) at hospital discharge indicates increasing mortality with decreasing ejection fraction. CHF = congestive heart failure; MI = myocardial infarction.

greater number of salvaged patients with relatively poor ventricular function may mask the overall gain in ejection fraction seen in other patients with reperfused coronary arteries and lower mean values for the entire group. However, the problems entailed in comparisons of survivors may not influence the prognostic value of the ejection fraction measurement itself. Others have argued (27) that ejection fraction may be of limited value because the compensatory noninfarct zone hyperkinesia often seen after infarction may lead to an augmentation of global measures.

**Comparison of TIMI II and MPRG data.** To compare our data with those obtained in the prethrombolytic era, the TIMI II cardiovascular mortality-left ventricular ejection fraction curve was compared with data from MPRG collected from 1979 to 1981 (1). There is strong evidence of a difference ( $p = 0.001$ ) between the survival curves of the two studies (Fig. 5). There were also clinical differences between the two groups (Table 4). The MPRG

patients had a smaller proportion of men and a higher prevalence of previous infarction, rates, heart rate  $\geq 90$  beats/min, ischemia during the hospital period and ejection fraction  $< 40\%$ . There was a higher prevalence of anterior infarction in the TIMI II cohort.

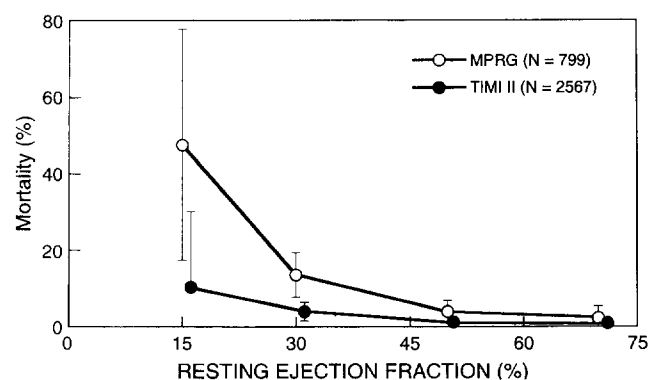
TIMI II involved more than three times the number of patients in MPRG. Clinical differences between groups were noted (Table 4). Despite clinical differences, the objective variable of measured ejection fraction was used to characterize the patients in both MPRG and TIMI II. The effect that the clinical differences would have on mortality is not likely to be as great as the impact of thrombolytic therapy and revascularization, where appropriate. However, there are limitations inherent in using historical control subjects. Many clinical and

**Table 4.** Patient Characteristics and Radionuclide Ventriculographic Prognosis

Characteristic	TIMI II n = 2,567 (%)	MPRG* n = 866 (%)	p Value
Baseline			
Male	84	78	$< 0.01$
Age $\geq 60$ yr	40	43	$> 0.10$
Prior MI	13	24	$< 0.001$
Anterior MI	51	36	$< 0.001$
Rates $\geq 1/3$ lung fields	3	14	$< 0.001$
Heart rate $\geq 90$ beats/min	19	23	$< 0.01$
Hospital course: ischemia*	24	33	$< 0.001$

\*Recurrent painful ischemic events in Thrombolysis in Myocardial Infarction (TIMI) II; angina in the Multicenter Postinfarction Research Group (MPRG). MI = myocardial infarction.

**Figure 5.** Comparison of cardiovascular mortality rate curves in relation to rest ejection fraction. Note the increased mortality in the Multicenter Postinfarction Research Group (MPRG) studies at the lower levels of ejection fraction. The data from the Thrombolysis in Myocardial Infarction Phase II trial (TIMI II) have been regrouped according to specifications outlined in the MPRG study (1). Vertical bars represent confidence intervals.



therapeutic factors have changed in the interim in addition to the utilization of thrombolytic therapy.

These data also suggest that in addition to preserving left ventricular myocardium, thrombolytic and associated therapies may enhance survival at any particular level of left ventricular function by other mechanisms. The explanation for this is not readily apparent. Selection of patients for thrombolytic therapy may be a factor in the low mortality observed. However, these observations may provide additional support for the "open artery hypothesis" (27-33). A number of relevant pathophysiologic phenomena may occur after prompt opening of the occluded artery that may improve survival but not necessarily global ventricular function. The open infarct-related artery, as may be anticipated after thrombolysis, may result in substantial alteration in early ventricular remodeling. Left ventricular infarct expansion may be limited. In addition, changes may occur through preservation of an epicardial rim of myocardium as well as through maintenance of effective diastolic properties of the left ventricle resulting from an open coronary artery (34). Thrombolysis may also have specific electrophysiologic effects that may influence mortality through prevention of major arrhythmias (35-38). After thrombolysis, infarcted tissue may be more homogeneous and may thus have improved electrical stability on this basis, independent of left ventricular function. Finally, there may be independent, still poorly defined effects of thrombolytic therapy on infarcted myocardium that may involve factors such as blood viscosity, alteration of collagenases and other cytoprotective effects (39-41). Concomitant therapy and appropriate revascularization for ischemia (provided according to the TIMI II protocol) may also have influenced survival.

**Conclusions.** This report emphasizes the continued prognostic value of rest left ventricular ejection fraction measurement before discharge in patients receiving thrombolytic therapy. Ejection fraction measurement should be considered along with other clinical variables previously defined in TIMI II (26,41-46). Despite relatively low mortality in the entire cohort, low ejection fraction measurements identify those patients with a poor prognosis. Because ejection fraction at rest <30% was associated with highest mortality, this finding might be considered a surrogate end point in clinical trials of thrombolysis. Those in whom measurements could not be obtained, for a variety of reasons, also experienced a poor outcome. Exercise measurement does not add to this prognostic assessment.

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